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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/632,150	07/30/2003	Dah Shiam Chiaur	5914-098-999	1870

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EXAMINER	
SHEN, WU CHENG WINSTON	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 12/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/632,150	CHIAUR ET AL.	
	Examiner	Art Unit	
	Wu-Cheng Winston Shen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *50-74* is/are pending in the application.

4a) Of the above claim(s) *56-74* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *50-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application 10/632,150 filed on July 30, 2003 is a DIV of 09/385,219 filed on 08/27/1999 patent No. 6720,181, which claims benefit of provisional applications 60/098,355 filed on 08/28/1998.

Election/Restriction

1. Applicant's election with traverse of Group I, claims 50-55, in the reply filed on Oct. 27, 2006 is acknowledged. The traversal is on the ground(s) that (i) applicants provisional elect, with traverse, to pursue the subject matter of the claims I, claims 50-55, (ii) applicants fully reserve the right to prosecute the subject matter of the non-elected inventions in one or more related applications, (iii) applicants retain the right to petition from the restriction requirement under 37 C.F.R. § 1.144. This is not found persuasive because applicants did not distinctly and specifically point out supposed errors in the restriction requirement.

The requirement is still deemed proper and is therefore made FINAL.

Claims 56-74 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. In the amended claims filed on July 30, 2003, applicant cancelled claims 1-49, which was also filed on July 30, 2003.

Status of claims: Claims 50-55 are currently under examination.

Claim Rejection - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

2. Claims 50-55 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

The claims are directed to (i) an isolated nucleic acid molecule comprising a nucleotide sequence which encodes a polypeptide comprising the amino acid sequence of SEQ ID NO: 10 (claim 50), (ii) an isolated nucleic acid molecule which encodes an F-box polypeptide, or a fragment thereof, said nucleic acid molecule comprising a nucleotide sequence of SEQ ID NO: 9 (claim 51), (iii) an isolated nucleic acid sequence derived from a mammalian genome hybridizes under highly stringent conditions to the nucleotide sequence of SEQ ID NO: 9; and encodes a gene product which contains an F-box motif and binds to Skp1 (claim 52), (iv) an expression vector containing the nucleotide sequence of Claim 50, 51 or 52, in operative association with a nucleotide regulatory sequence that controls expression of the nucleotide sequence in a host cell, and (v) a genetically engineered host cell that contains the nucleotide sequence of Claim 50, 51 or 52, in operative association with a nucleotide regulatory sequence that controls expression of the nucleotide sequence in the host cell.

The claimed invention is directed to a nucleotide sequence that encodes a novel human F-box protein, FBP5. The specification has asserted that the nucleotide sequence set forth in SEQ ID NO: 9 encodes a novel human substrate-targeting subunit of ubiquitin ligase, comprising, F-box motif, having the amino acid sequence set forth in SEQ ID NO: 10. The disclosed utilities

for the nucleotide sequence set forth in SEQ ID NO: 9 (as well as fragments of SEQ ID NO:9, variants of SEQ ID NO:9, nucleotide sequences that hybridize to SEQ ID NO:9, vectors comprising any of the same nucleotide sequences, pharmaceutical compositions comprising any of the same nucleotide sequences, and host cells comprising any of the same nucleotide sequences) include the diagnosis, screening of compounds for prevention and treatment of diseases associated with expression of same novel human ubiquitin ligase.

However, the specification fails to provide a specific and substantial utility for the claimed nucleotide sequences or the polypeptides that they encode. Neither the specification nor any art of record teaches what the polynucleotide of SEQ ID NO: 9 does or, in the case of pharmaceutical compositions, establishes a relationship of the polynucleotide of SEQ ID NO: 9 to any specific disease or establishes any involvement of the polynucleotide of SEQ ID NO: 9 in the etiology of any specific disease. Although the specification has contemplated that the claimed sequences may be related to any of the diseases associated with ubiquitin ligase recited on pages 68-69, no evidence has been presented that relates the claimed sequences to even one of the recited diseases.

A substantial utility is a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities under §101. Applicant's specification fails to provide a "real world" use of the polypeptide set forth in SEQ ID NO: 9 such that the nucleic acid set forth in SEQ ID NO: 9 that encodes the unspecified protein additionally has no "real world" use. Neither the specification as filed, nor any art of record disclose or suggest any biological or biochemical activity for the protein encoded by SEQ ID NO: 9 such that any utility would be well established

for the protein. The asserted utilities for SEQ ID NO:9 such as a probe for diagnosing a disease, primers for PCR, treatment of disease is merely a "potential" use that applies to any uncharacterized, unrelated polynucleotide sequences. Therefore the asserted utilities are not considered "specific" utilities, i.e. they are not specific to SEQ ID NO:9.

The asserted utility of SEQ ID NO:9 is based on the assertion that SEQ ID NO:9 has sequence homology to a sequence encoding a known ubiquitin ligase. The specification has merely provided sequence homology information in the F-box motif, however, it is unclear whether the mere presence of homology to F-box motif encoded SEQ ID NO: 9 would be sufficient to assert that SEQ ID NO 9 does encode a functional ubiquitin ligase. Moreover, the specification has failed to provide evidence of any *structural* elements, that are related to ubiquitin ligase in general, that may be present within the claimed sequence to support such assertions. In any event, assuming the assertions of the instant specification are correct and that SEQ ID NO: 9 encodes an ubiquitin ligase of some kind, it is unclear exactly which type of ubiquitin ligase is encoded by the claimed sequence, or what substrates the putative ubiquitin ligase acts on. The superfamily of ubiquitin ligase is comprised of many members, which have different chemical structures, different tissue specificities, different activators and inhibitors, and more importantly different substrates for proteolysis. The specification (see pages 1-4) and the state of the art teaches the variability function between three classes of the known human ubiquitin ligases, (i) N-end rule ubiquitin ligases, (ii) HECT E3 ubiquitin ligases, (iii) Really Interesting New Gene (RING) family ubiquitin ligases, which belongs to SCF (Skp1-Cullin-F-box) E3 ubiquitin ligases. For instance, Sun reviewed ubiquitin ligase family and stated that there are approximately 1000 E3 ligases in the human genome that can be classified into three

major types, based on their domain structure and substrate recognition. The first class comprises N-end rule ubiquitin ligases that target protein substrates bearing specific destabilizing N-terminal residues, including Arg, Lys, His (type I), and Phe, Trp, Leu, Tyr, and Ile (type II). One recent example of protein degradation by the Ub-dependent N-end rule pathway is *Drosophila* inhibitor of apoptosis protein (IAP). The second type of E3 is HECT, with the first family member being E6-associated protein (E6-AP), which, together with oncoprotein E6, promotes p53 ubiquitination and degradation. HECT E3 ligases contain an approximately 350–amino acid C-terminal region homologous to that of E6-AP, with a conserved active-site cysteine residue near the C-terminus, through which HECT domain E3 ligases form thioester intermediates with Ub. N-terminal regions are highly variable and may be involved in substrate recognition. The third and largest type of E3 ligase is the Really Interesting New Gene (RING) family, which contains a classic C3H2C3 or C3HC4 RING finger domain with a characteristic linear sequence of Cys-X2-Cys-X9–39-Cys-X1–3-His-X2–3-Cys/His-X2-Cys-X4–48-Cys-X2-Cys, where X can be any amino acid. A RING finger domain binds to two zinc atoms per molecule in a cross-braced system, where the first and third pairs of cysteine/histidine form the first binding site and where the second and fourth pairs of cysteine/histidine form the other (See Sun, bridging paragraph pages 645-646, E3 ubiquitin ligases as cancer targets and biomarkers. *Neoplasia.* 8(8): 645-54, 2006).

With regard to eukaryotic F-box proteins, Ho et al stated, the eukaryotic protein degradation pathway involves the ubiquitin (Ub) modification of substrates targeted for degradation by the 26S proteasome. The addition of Ub, a process called ubiquitination, is mediated by enzymes including the E3 Ub ligases, which transfer the Ub to targeted substrates.

A major type of E3 Ub ligases, the SCF (Skp–Cullin–F-box) complex, is composed of four major components: Skp1, Cul1/Cdc53, Roc1/Rbx1/Hrt1, and an F-box protein. The F-box component of the SCF machineries is responsible for recognizing different substrates for ubiquitination. Interaction with components of the SCF complex is mediated through the F-box motif of the F-box protein while it associates with phosphorylated substrates through its second protein–protein interaction motif such as Trp–Asp (WD) repeats or leucine-rich repeats (LRRs). By targeting diverse substrates, F-box proteins exert controls over stability of proteins and regulate the mechanisms for a wide-range of cellular processes. Ho et al. discuss the importance of F-box proteins by providing a general overview and examples of how F-box proteins function in various cellular settings such as tissue development, cell proliferation, and cell death, in the modeling organism *Drosophila* (See abstract, Ho et al., F-box proteins: the key to protein degradation. *J Biomed Sci.* 13(2): 181-91, 2006).

These references demonstrate the biochemical diversity between ubiquitin ligase superfamily members. However, neither the specification nor any art of record has taught what type of ubiquitin ligase is encoded by SEQ ID NO: 9 or which substrates it proteolyses leaving the skilled artisan to speculate and investigate the uses of the uncharacterized lipase. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed nucleic acids and the proteins they encode. In view of the lack of guidance with respect to the type of ubiquitin ligase the claimed invention encompasses, the skilled artisan would not know how to use the claimed nucleotide sequence or its expression product. Because the claimed invention is not supported by a specific asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

Claim Rejection - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 52-55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to an isolated nucleic acid sequence derived from a mammalian genome hybridizes under highly stringent conditions to the nucleotide sequence of SEQ ID NO: 9; and encodes a gene product which contains an F-box motif and binds to Skp1 (claim 52). The claims are further directed to an expression vector containing the nucleotide sequence of claim 52, in operative association with a nucleotide regulatory sequence that controls expression of the nucleotide sequence in a host cell. The claims are further directed to a genetically engineered host cell that contains the nucleotide sequence of claim 52, in operative association with a nucleotide regulatory sequence that controls expression of the nucleotide sequence in the host cell. Particular claim embodiments are directed to isolated nucleic acid sequence derived from a mammalian genome hybridizes under highly stringent conditions to the nucleotide sequence of SEQ ID NO: 9; and encodes a gene product which contains an F-box motif and binds to Skp1.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

The DNA sequences of from all mammals that hybridizes under highly stringent conditions to the nucleotide sequence of SEQ ID NO: 9; and encodes a gene product which contains an F-box motif and binds to Skp1 are encompassed within the genus of isolated nucleic acid that have not been disclosed. Based upon the prior art there is expected to be sequence variation among the species of DNA sequences of all mammal that hybridizes under highly stringent conditions to the nucleotide sequence of SEQ ID NO: 9; and encodes a gene product which contains an F-box motif and binds to Skp1. The specification suggests that the SEQ ID NO 9 encodes a human F-box protein (FBP), FBP5, which interacts with tagged Skp1 *in vitro* (see Fig. 29) and endogenous Skp1 biochemically (see Fig. 30). The specification has also contemplated that the putative protein-protein interaction domains in human FBPs may be contained within recited SEQ ID numbers (See Fig. 2). The specification however has not disclosed the sequences of any DNA sequences of from all mammals that are essential for hybridization under highly stringent conditions to the nucleotide sequence of SEQ ID NO: 9; and encoding a gene product which contains an F-box motif and binds to Skp1. There is no evidence on the record of a relationship between the structures of the DNA molecules of any of the

embraced mammalian DNA sequences that would provide any reliable information about the structure of DNA molecules within the genus. There is no evidence on the record that embraced sequences of any DNA sequences of from all mammals that are essential for hybridization under highly stringent conditions to the nucleotide sequence of SEQ ID NO: 9; and encoding a gene product which contains an F-box motif and binds to Skp1, had known structural relationships to each other; the art indicated that there is variation between DNA sequences of various mammalian DNA sequences that may hybridize under highly stringent conditions to the nucleotide sequence of SEQ ID NO: 9; and encoding a gene product which contains an F-box motif and binds to Skp1 . The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which is not conventional in the art as of applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998).

In the instant case the claimed embodiments of an isolated nucleic acid sequence derived from a mammalian genome hybridizes under highly stringent conditions to the nucleotide sequence of SEQ ID NO: 9; and encodes a gene product which contains an F-box motif and binds to Skp 1 lack a written description. The specification fails to describe what DNA molecules fall into this genus. The skilled artisan cannot envision the detailed chemical structure of the encompassed regulatory elements, and therefore conception is not achieved until reduction

to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of the above considerations one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by member of the genus of nematode regulatory elements. Moreover, the art has recognized that there would be variation among the species of the genus of DNA sequences of mammal as such DNA sequences appear to be specific for particular genes from different species of mammal. Therefore, Applicant was not in possession of the genus of all DNA sequences of from all mammals that hybridizes under highly stringent conditions to the nucleotide sequence of SEQ ID NO: 9; and encodes a gene product which contains an F-box motif and binds to Skp1 as encompassed by the claims. University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention."

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

4. The term "highly stringent conditions" in claim 52 is a relative term, which renders the claim indefinite. The term " highly stringent conditions " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention.

It is unclear what it means by "hybridizes under highly stringent conditions". The specification fails to define the term "highly stringent conditions", thereby fails to particularly point out and distinctly claim the subject matter which applicant regards as the invention with regard to the metes and bounds of "highly stringent conditions" used for performing hybridization.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 51-55 are rejected under 35 U.S.C. 102(b) as being anticipated by NCI-CGAP http://www.ncbi.nlm.nih.gov/ncicgap (See National Cancer Institute, Cancer Genome Anatomy Project (CGAP), Tumor Gene Index, 1997).

NCI-CGAP http://www.ncbi.nlm.nih.gov/ncicgap teaches a *cDNA clone* of Rhesus monkey (*Macaca multta*) that matches the SEQ ID 9, with SEQ ID 9 nucleotide Nos from 605 to 1329 being 98.3% identical to the nucleotide sequences from 3 to 727 of NCI-CGAP http://www.ncbi.nlm.nih.gov/ncicgap database (See below for details of the sequence search result and alignment).

With regard to the limitation "encodes a gene product which contains an F-box motif and binds to Skp1" (claim 52), the coding sequence of F-box motif of SEQ ID 9 ranges from nucleotide numbers 809-939 (CTC TTT----------TTC CAG, encoding amino acid residues 250-294 of SEQ ID 10, Leu Phe----------Phe Gln) and this region is encompassed by the cDNA clone of Rhesus monkey (*Macaca multta*)

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RESULT 15
CB229742
LOCUS       CB229742                733 bp    mRNA    linear   EST 10-FEB-2003
DEFINITION  AGENCOURT_11571875 NICHD_Rh_Ov1 Macaca mulatta cDNA clone
            IMAGE:6882476 5', mRNA sequence.
ACCESSION   CB229742
VERSION     CB229742.1  GI:28281320
KEYWORDS    EST.
SOURCE      Macaca mulatta (rhesus monkey)
  ORGANISM  Macaca mulatta
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Euarchontoglires; Primates; Catarrhini;
            Cercopithecidae; Cercopithecinae; Macaca.
REFERENCE   1  (bases 1 to 733)
  AUTHORS   NCI-CGAP http://www.ncbi.nlm.nih.gov/ncicgap.
  TITLE     National Cancer Institute, Cancer Genome Anatomy Project (CGAP),
            Tumor Gene Index
  JOURNAL   Unpublished (1997)
COMMENT     Contact: Robert Strausberg, Ph.D.
            Email: cgapbs-r@mail.nih.gov
            Tissue Procurement: Dr. Eliot Spindel
             cDNA Library Preparation: CLONTECH
             cDNA Library Arrayed by: The I.M.A.G.E. Consortium (LLNL)
             DNA Sequencing by: Agencourt Bioscience Corporation
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            Clone distribution: NCI-CGAP clone distribution information can be
            found through the I.M.A.G.E. Consortium/LLNL at:
            http://image.llnl.gov
            Plate: LLCM3129  row: c  column: 19
            High quality sequence stop: 655.
FEATURES              Location/Qualifiers
     source           1. .733
                      /organism="Macaca mulatta"
                      /mol_type="mRNA"
                      /db_xref="taxon:9544"
                      /clone="IMAGE:6882476"
                      /tissue_type="Ovary"
                      /lab_host="DH10B (phage-resistant)"
                      /clone_lib="NICHD_Rh_Ov1"
                      /note="Organ: ovary; Vector: pDNR-LIB; Site_1: Sfi I;
                      Site_2: Sfi I; Cloned unidirectionally. Primer: Oligo dT.
                      Average insert size 1.0-4.0 kb. Tissue pooled from
                      pre-pubertal, post pubertal sn menopausal monkeys.
                      Constructed by Clontech. Note: this is a NICHD Library."
ORIGIN

  Query Match             34.0%;  Score 705.8;  DB 4;  Length 733;
  Best Local Similarity   98.3%;  Pred. No. 1e-131;
  Matches  713;  Conservative    0;  Mismatches   12;  Indels    0;  Gaps    0;

Qy        605 AGCCCAGACCAATATCCCAACAAAAACTTGCTGCCAGTTCTTCATTTTGAAAAAGTGGTT 664
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          3 AGCCCAGACCAATATCCCAACAAAAACTTGCTGCCAGTTCTTCATTTTGAAAAAGTGGTT 62

Qy        665 TGTTCAACATTAAAAAAGAATGCAAAACGAAATCCTAAAGTAGATCGGGAGATGCTGAAG 724
              |||||||||||||||||||||||| ||||||||||||||||||||||||||||||||||
Db         63 TGTTCAACATTAAAAAAGAATGCAAAGCGAAATCCTAAAGTAGATCGGGAGATGCTGAAG 122

Qy        725 GAAATTATAGCCAGAGGAAATTTTAGACTGCAGAATATAATTGGCAGAAAAATGGGCCTA 784
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        123 GAAATTATAGCCAGAGGAAATTTTAGACTGCAGAATATAATTGGCAGAAAAATGGGCCTA 182

Qy        785 GAATGTGTAGATATTCTCAGCGAACTCTTTCGAAGGGGACTCAGACATGTCTTAGCAACT 844
              |||||||||||||||||||||||||||||||||||||||||||||| ||||||||||||
Db        183 GAATGTGTAGATATTCTCAGCGAACTCTTTCGAAGGGGACTCAGACATCTCTTAGCAACT 242

Qy        845 ATTTTAGCACAACTCAGTGACATGGACTTAATCAATGTGTCTAAAGTGAGCACAACTTGG 904
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        243 ATTTTAGCACAACTCAGTGACATGGACTTAATCAATGTGTCTAAAGTGAGCACAACTTGG 302

Qy        905 AAGAAGATCCTAGAAGATGATAAGGGGGCATTCCAGTTGTACAGTAAAGCAATACAAAGA 964
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        303 AAGAAGATCCTAGAAGATGATAAGGGGGCATTCCAGTTGTACAGTAAAGCAATACAAAGA 362

Qy        965 GTTACCGAAAACAACAATAAATTTTCACCTCATGCTTCAACCAGAGAATATGTTATGTTC 1024
              |||||||||||||||||||||||||| ||||| |||||||||||| |||||||||||
Db        363 GTTACCGAAAACAACAATAAATTTTCACCACATGCGTCAACCAGAGAATTTGTTATGTTC 422

Qy       1025 AGAACCCCACTGGCTTCTGTTCAGAAATCAGCAGCCCAGACTTCTCTCAAAAAAGATGCT 1084
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        423 AGAACCCCACTGGCTTCTGTTCAGAAATCAGCAGCCCAGACTTCTCTCAAAAAAGATGCT 482

Qy       1085 CAAACCAAGTTATCCAATCAAGGTGATCAGAAAGGTTCTACTTATAGTCGACACAATGAA 1144
              |||||||| |||||||||||||||||||| |||||||||||||||||||||||||||||
Db        483 CAAACCAAGGTATCCAATCAAGGTGATCAGAAGGGTTCTACTTATAGTCGACACAATGAA 542
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Qy       1145 TTCTCTGAGGTTGCCAAGACATTGAAAAAGAACGAAAGCCTCAAAGCCTGTATTCGCTGT 1204
              ||||||||||||||||||| |||||||||| ||||||||||||||||||||||||||
Db        543 TTCTCTGAGGTTGCCAAGACTTTGAAAAAGAATGAAAGCCTCAAAGCCTGTATTCGCTGT 602

Qy       1205 AATTCACCTGCAAAATATGATTGCTATTTACAACGGGCAACCTGCAAACGAGAAGGCTGT 1264
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        603 AATTCACCTGCAAAATATGATTGCTATTTACAACGGGCAACCTGCAAACGAGAAGGCTGT 662

Qy       1265 GGATTTGATTATTGTACGAAGTGTCTCTGTAATTATCATACTACTAAAGACTGTTCAGAT 1324
              ||||||||||||||||||||||| |||||||| |||||||| ||||||||||||||
Db        663 GGATTTGATTATTGTACGAAGTGTCTATGTAATTACCATACTACCAAAGACTGTTCAGAT 722

Qy       1325 GGCAA 1329
              |||||
Db        723 GGCAA 727
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6. Claims 51-55 are rejected under 35 U.S.C. 102(b) as being anticipated by Bonaldo et al. (See sequence search result listed below, Bonaldo et al. Normalization and subtraction: two approaches to facilitate gene discovery. *Genome Res.* 6 (9), 791-806, 1996).

Bonaldo et al teach that large-scale sequencing of cDNAs randomly picked from libraries has proven to be a very powerful approach to discover (putatively) expressed sequences that, in turn, once mapped, may greatly expedite the process involved in the identification and cloning of human disease genes. With the goal of facilitating such efforts, Bonaldo et al. teach a method to construct directionally cloned normalized cDNA libraries and applied it to generate infant brain (INIB) and fetal liver/spleen (INFLS) libraries, from which a total of 45,192 and 86,088 expressed sequence tags, respectively, have been derived. While improving the representation of the longest cDNAs in our libraries, Bonaldo et al. teach three additional methods to normalize cDNA libraries and generated over 35 libraries, most of which have been contributed to our integrated Molecular Analysis of Genomes and Their Expression (IMAGE) Consortium and thus distributed widely and used for sequencing and mapping. In an attempt to facilitate the process of gene discovery further, Bonaldo et al. also teach a subtractive hybridization approach designed

specifically to eliminate (or reduce significantly the representation of) large pools of arrayed and (mostly) sequenced clones from normalized libraries yet to be (or just partly) surveyed.

With regard to the expression of SEQ ID No 9, or a fragment thereof (claim 51-52) and expression vector and host cell (claims 53-55), Bonaldo et al. teach a comparative analysis of four methods that Bonaldo et al. had developed and used to generate normalize cDNA libraries from human (15), mouse (3), rat (2), as well as the parasite *Schistosoma mansoni*. Bonaldo et al. also teach the construction and preliminary characterization of a subtracted liver/spleen library (INFLS-SI) that resulted from the elimination (or reduction of representation) of -5000 INFLS-IMAGE clones from the INFLS library (See abstract).

The details of nucleic acid sequence search of SEQ ID No. 9 aligned with the human nucleic acid sequences taught by Bonaldo et al. are listed below.

```
RESULT 13
BM675277/c
LOCUS       BM675277                746 bp    mRNA    linear   EST 27-FEB-2002
DEFINITION  UI-E-EJ0-ahr-1-01-0-UI.s1 UI-E-EJ0 Homo sapiens cDNA clone
            UI-E-EJ0-ahr-1-01-0-UI 3', mRNA sequence.
ACCESSION   BM675277
VERSION     BM675277.1  GI:18985175
KEYWORDS    EST.
SOURCE      Homo sapiens (human)
  ORGANISM  Homo sapiens
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Euarchontoglires; Primates; Catarrhini;
            Hominidae; Homo.
REFERENCE   1  (bases 1 to 746)
  AUTHORS   Bonaldo,M.F., Lennon,G. and Soares,M.B.
  TITLE     Normalization and subtraction: two approaches to facilitate gene
            discovery
  JOURNAL   Genome Res. 6 (9), 791-806 (1996)
   PUBMED   8889548
COMMENT     Contact: Soares, MB
            Coordinated Laboratory for Computational Genomics
            University of Iowa
            375 Newton Road , 4156  MEBRF, Iowa City, IA 52242, USA
            Tel: 319 335 8250
            Fax: 319 335 9565
            Email: bento-soares@uiowa.edu
            Tissue Procurement: Dr. Gregg Hageman
```

cDNA Library preparation: Dr. M. Bento Soares, Univeristy of Iowa
cDNA Library Arrayed by: Dr. M. Bento Soares, Univeristy of Iowa
DNA Sequencing by: Dr. M. Bento Soares, Univeristy of Iowa
Clone Distribution: Researchers may obtain clones from Research Genetics (www.resgen.com).
The following repetitive elements were found in this cDNA sequence: 421-501, >AT_rich#Low_complexity (matched compliment)
Seq primer: M13 Forward
POLYA=Yes.

FEATURES Location/Qualifiers
source 1. .746
/organism="Homo sapiens"
/mol_type="mRNA"
/db_xref="taxon:9606"
/clone="UI-E-EJ0-ahr-l-01-0-UI"
/tissue_type="fetal eyes, lens, eye anterior segment, optic nerve, retina, Retina Foveal and Macular, RPE and Choroid"
/dev_stage="fetal and adult"
/lab_host="DH10B (Life Technologies) (T1 phage resistant)"
/clone_lib="UI-E-EJ0"
/note="Organ: eye; Vector: pT7T3-Pac (Pharmacia) with a modified polylinker; Site_1: EcoR I; Site_2: Not I; UI-E-EJ0 is a subtracted cDNA library constructed according to Bonaldo, Lennon and Soares, Genome Research, 6:791-806, 1996. First strand cDNA synthesis was primed with an oligo-dT primer containing a Not I site. Double stranded cDNA was ligated to an EcoR I adaptor, digested with Not I, and cloned directionally into pT7T3-Pac vector. The oligonucleotide used to prime the synthesis of first-strand cDNA contains a library tag sequence that is located between the Not I site and the (dT)18 tail. The sequence tags for this library are: fetal eyes, AGAATCAAGA; lens, CGATTAGCGA; eye anterior segment, AATGCCGCAT; optic nerve, CCATTAAGTG; retina, CCGCG; Retina Foveal and Macular, GTCC; RPE and Choroid, ACCTA. This library was created for the program, Gene Discovery in the Visual System, supported by National Eye Institute (NEI).
TAG_TISSUE=human retina
TAG_LIB=UI-E-EJ0
TAG_SEQ=CCGCG"

ORIGIN

Query Match 34.7%; Score 720.2; DB 3; Length 746;
Best Local Similarity 99.5%; Pred. No. 1.3e-134;
Matches 733; Conservative 0; Mismatches 3; Indels 1; Gaps 1;

```
Qy       1326 GCAAGCTCCTCAAAGCCAGTTGTAAAATAGGTCCCCTGCCTGGTACAAAGAAAAGCAAAA 1385
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        741 GCAAGCTCCTCAAAGCCAGTTGTAAAATAGGTCCCCTGCCTGGTACAAAGAAAAGCAAAA 682

Qy       1386 AGAATTTACGAAGATTGTGATCTCTTATTAAATCAATTGTTACTGATCATGAATGTTAGT 1445
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        681 AGAATTTACGAAGATTGTGATCTCTTATTAAATCAATTGTTACTGATCATGAATGTTAGT 622

Qy       1446 TAGAAAATGTTAGGTTTTAACTTAAAAAAAATTGTATTGTGATTTTCAATTTTATGTTGA 1505
             ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        621 TAGAAAATGTTAGGTTTTAACTTAAAAAAAATTGTATTGTGATTTTCAATTTTATGTTGA 562

Qy       1506 AATCGGTGTAGTATCCTGAGGTTTTTTTCCCCCCAGAAGATAAAGAGGATAGACAACCTC 1565
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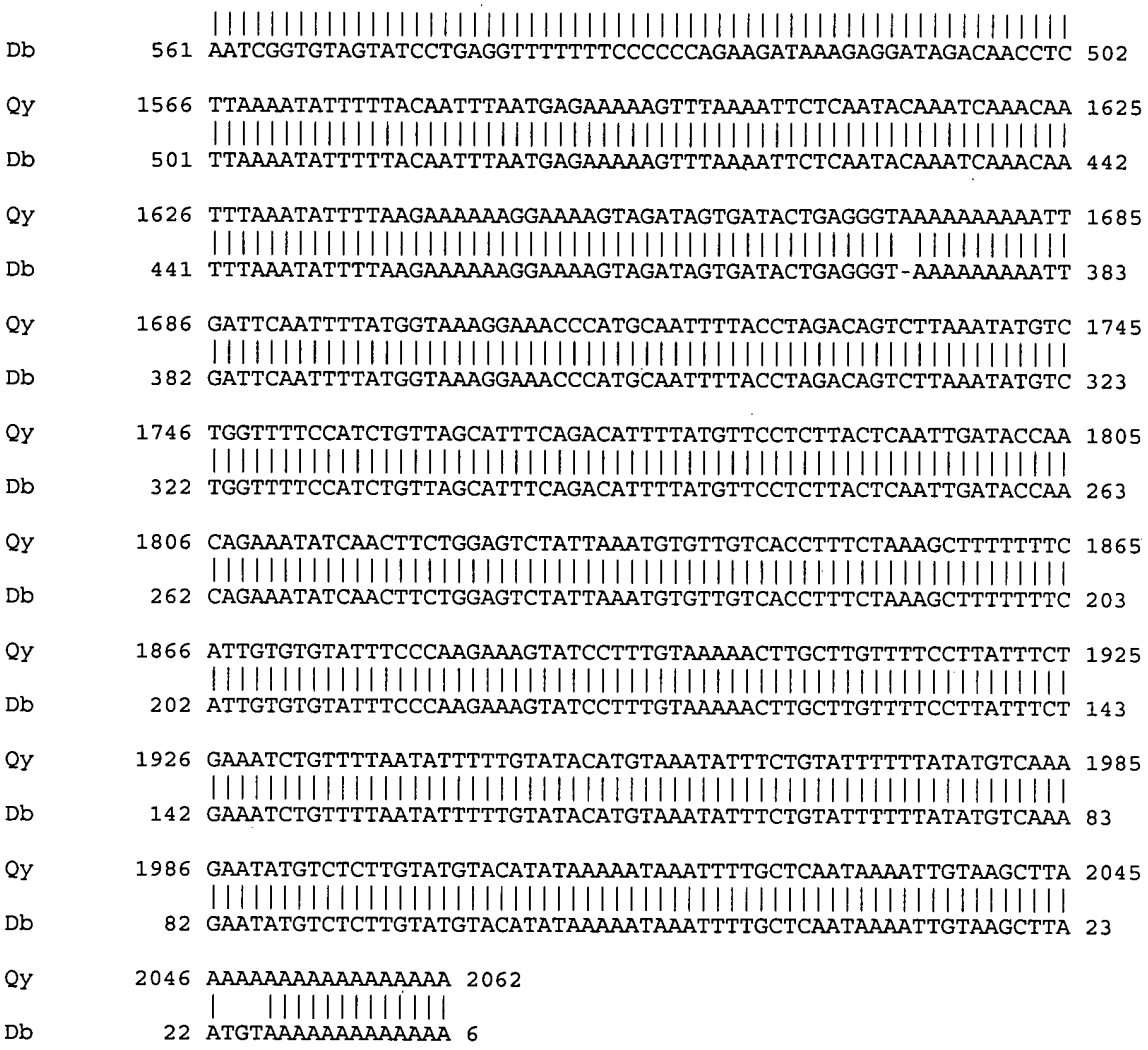

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 51-55 are rejected under 35 U.S.C. 102(e) as being anticipated by Williams et al (U.S. application No. 09/297,648, U.S. Patent No. 6,964,868, date of Patent, Nov. 15, 2005, which is an U.S. application No. 09/297,648. The application is the National Phase under 35 U.S.C. 371 of International Application No. PCT/US99/01619, filed Jan. 28, 1999, which International Application was published by the International Bureau in English on Aug. 5, 1999, which International Application claims the benefit of U.S. provisional patent application Ser. No. 60/072,910, filed Jan. 28, 1998; U.S. provisional patent application Ser. No. 60/075,954, filed Feb. 24, 1998; U.S. provisional patent application Ser. No. 60/080,114, filed Mar. 31, 1998; U.S. provisional patent application Ser. No. 60/080,515, filed Apr. 3, 1998; U.S. provisional patent application Ser. No. 60/080,666, filed Apr. 3, 1998; U.S. provisional patent application Ser. No. 60/105,234, filed Oct. 21, 1998; and of U.S. provisional patent application Ser. No. 60/105,877, filed Oct. 27, 1998).

Williams et al. teach novel human polynucleotides and variants thereof, their encoded polypeptides and variants thereof, to genes corresponding to these polynucleotides and to proteins expressed by the genes. Williams et al. also teach diagnostic and therapeutic agents employing such novel human polynucleotides, their corresponding genes or gene products, e.g., these genes and proteins, including probes, antisense constructs, and antibodies.

With regard to the expression of SEQ ID No 9, or a fragment thereof (claim 51-52 of instant application), Williams et al. teach a SEQ ID No. 4117 that matches the SEQ ID 9 of instant application, with SEQ ID 9 nucleotide numbers ranging from 712 to 1220 being 88.4%

identical to the nucleotide sequences from 68 to 576 of the SEQ ID No. 4117 taught by Williams et al (See details of sequence alignment listed below).

With regard to the limitation "encodes a gene product which contains an F-box motif and binds to Skp1" (claim 52 of instant application), the coding sequence of F-box motif of SEQ ID 9 ranges from nucleotide numbers 809-939 (CTC TTT----------TTC CAG, encoding amino acid residues 250-294 of SEQ ID 10, Leu Phe----------Phe Gln) and this region is encompassed by the SEQ ID No. 4117 of a human gene taught by Williams et al.

With regard to expression vector, host cell (claims 53-55 of instant application), Williams teach vector and host cell (See claims 2,3 8, and 9, Williams et al.)

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RESULT 5
US-09-297-648-4117
; Sequence 4117, Application US/09297648
; Patent No. 6964868
; GENERAL INFORMATION:
;  APPLICANT:  Williams, Lewis T.
;  APPLICANT:  Escobedo, Jaime
;  APPLICANT:  Innis, Michael A.
;  APPLICANT:  Garcia, Pablo Dominiguez
;  APPLICANT:  Sudduth-Klinger, Julie
;  APPLICANT:  Reinhard, Christoph
;  APPLICANT:  Giese, Klause
;  APPLICANT:  Randazzo, Filippo
;  APPLICANT:  Kennedy, Giulia C.
;  APPLICANT:  Pot, David
;  APPLICANT:  Kassan, Altaf
;  APPLICANT:  Lamson, George
;  APPLICANT:  Drmanac, Radoje
;  APPLICANT:  Crkvenjakov, Radomir
;  APPLICANT:  Dickson, Mark
;  APPLICANT:  Drmanac, Snezana
;  APPLICANT:  Labat, Ivan
;  APPLICANT:  Leshkowitz, Dena
;  APPLICANT:  Kita, David
;  APPLICANT:  Garcia, Veronica
;  APPLICANT:  Jones, William Lee
;  APPLICANT:  Stache-Crain, Birjit
;  TITLE OF INVENTION:  No. 6964868el Human Genes and Gene Expression
;  TITLE OF INVENTION:  Products II
;  FILE REFERENCE:  2300-1481
;  CURRENT APPLICATION NUMBER: US/09/297,648
;  CURRENT FILING DATE:  2000-03-10
;  PRIOR APPLICATION NUMBER:  60/072,910
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;  PRIOR FILING DATE:  1998-01-28
;  PRIOR APPLICATION NUMBER:  60/075,954
;  PRIOR FILING DATE:  1998-02-24
;  PRIOR APPLICATION NUMBER:  60/080,666
;  PRIOR FILING DATE:  1998-04-03
;  PRIOR APPLICATION NUMBER:  60/080,515
;  PRIOR FILING DATE:  1998-04-03
;  PRIOR APPLICATION NUMBER:  60/080,114
;  PRIOR FILING DATE:  1998-03-31
;  PRIOR APPLICATION NUMBER:  60/105,234
;  PRIOR FILING DATE:  1998-10-21
;  NUMBER OF SEQ ID NOS:  5252
;  SOFTWARE:  FastSEQ for Windows Version 4.0
; SEQ ID NO 4117
;   LENGTH: 817
;   TYPE: DNA
;   ORGANISM: Homo sapiens
;   FEATURE:
;   NAME/KEY: misc_feature
;   LOCATION: (1)...(817)
;   OTHER INFORMATION: n = A,T,C or G
US-09-297-648-4117

  Query Match             20.2%;  Score 420;  DB 4;  Length 817;
  Best Local Similarity   88.4%;  Pred. No. 2.4e-90;
  Matches  450;  Conservative    0;  Mismatches   59;  Indels    0;  Gaps    0;

Qy        712 GGAGATGCTGAAGGAAATTATAGCCAGAGGAAATTTTAGACTGCAGAATATAATTGGCAG 771
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         68 GGAGATGCTGAAGGAAATTATAGCCAGAGGAAATTTTAGACTGCAGAATATAATTGGCAG 127

Qy        772 AAAAATGGGCCTAGAATGTGTAGATATTCTCAGCGAACTCTTTCGAAGGGGACTCAGACA 831
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        128 AAAAATGGGCCTAGAATGTGTAGATATTCTCAGCGAACTCTTTCGAAGGGGACTCAGACA 187

Qy        832 TGTCTTAGCAACTATTTTAGCACAACTCAGTGACATGGACTTAATCAATGTGTCTAAAGT 891
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        188 TGTCTTAGCAACTATTTTAGCACAACTCAGTGACATGGACTTAATCAATGTGTCTAAAGT 247

Qy        892 GAGCACAACTTGGAAGAAGATCCTAGAAGATGATAAGGGGGCATTCCAGTTGTACAGTAA 951
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        248 GAGCACAACTTGGAAGAAGATCCTAGAAGATGATAAGGGGGCATTCCAGTTGTACAGTAA 307

Qy        952 AGCAATACAAAGAGTTACCGAAAACAACAATAAATTTTCACCTCATGCTTCAACCAGAGA 1011
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        308 AGCAATACAAAGAGTTACCGAAAACAACAATAAATTTTCACCTCATGCTTCAACCAGAGA 367

Qy       1012 ATATGTTATGTTCAGAACCCCACTGGCTTCTGTTCAGAAATCAGCAGCCCAGACTTCTCT 1071
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        368 ATATGTTATGTTCAGAACCCCACTGGCTTCTGTTCAGAAATCAGCAGCCCAGACTTCTCT 427

Qy       1072 CAAAAAAGATGCTCAAACCAAGTTATCCAATCAAGGTGATCAGAAAGGTTCTACTTATAG 1131
              |||||||||||||||||||||||||||||||||||||||||| | ||||||||| |
Db        428 CAAAAAAGATGCTCAAACCAAGTTATCCAATCAAGGTGATCAGAAANGGTCTACTTATTG 487

Qy       1132 TCGACACAATGAATTCTCTGAGGTTGCCAAGACATTGAAAAAGAACGAAAGCCTCAAAGC 1191
              ||              | |   |  |       |     |  |||  ||   |  |||||
Db        488 TCCGACACCATNGAANTNTTTTGAGGGTTGCNAAANACCATTGAAAAAAGAACNAAAAGC 547

Qy       1192 CTGTATTCGCTGTAATTCACCTGCAAAAT 1220
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                ||  |    |     ||| | || ||| |
Db        548 CTTAAAAGCCCTGTNTTCNCTTGTAAATT 576
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Conclusion

8. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to Dianiece Jacobs whose telephone number is (571) 272-0532.

PETER PARAS, Jr.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Wu-Cheng Winston Shen, Ph. D.
Patent Examiner
Art Unit 1632